INTOXICATION WITH PYRAZOLONES

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1 About 50 severe or fatal (mostly accidental) cases of intoxication in children by pyrazolones have been reported in the German literature of the past 59 years.

2 Characteristic symptoms are impaired consciousness progressing to coma and convulsions. In addition, sudden apnoea and cardiac arrest may occur. Hepatic lesions may develop after a latent period of 12–24 hours.

3 Haemoperfusion seems to be the only therapeutic measure which is able to reduce the total body load of all pyrazolones to a toxicologically relevant extent. Actual clinico-toxicological data from poisoned patients are not available as yet; however, distribution volumes, plasma half-lives and endogenous plasma clearances as well as removal kinetics *in vitro* of aminophenazone (aminopyrine), propyphenazone, metamizole (dipyrone), phenylbutazone and oxyphenbutazone as point to the efficacy of haemoperfusion with amberlite XAD-4 resin.

Introduction

THE incidence of intoxication with mild analgesics shows regional variation. In the Federal Republic of Germany intoxication with pyrazolones is common. Children are almost exclusively involved. They take these analgesics out of curiosity or they mistake them for sweets or they are given excessive therapeutic doses by their parents (v. Mühlendahl & Krienke, 1979). Two pyrazolone derivatives are on the market (propyphenazone, metamizole [dipyrone]) and two pyrazolidine derivatives (phenyl-butazone, oxyphenbutazone). The pyrazoline, aminophenazone (aminopyrine), which was most commonly used in West Germany for more than 80 years, was withdrawn from the market in 1978 because of the problem of nitrosation and carcinogenicity and it was replaced by propyphenazone. Pyrazolones and their most important German proprietary names are given in Table 1.

Size of the problem

Intoxication with mild analgesics is common, and these drugs account for 6–15% of acute drug intoxications in West Germany (v. Mühlendahl & Krienke, 1978; Okonek, 1978). Severe and fatal intoxication with pyrazolones is rare. In the German literature of the past 59 years about 50 cases have been described (review of case reports until 1967 in Ibe, Beyer, Burmeister & Grosser, 1967; Geldmacher-v. Mallinckrodt, Geldmacher & Muller, 1971; Havers & Stolecke, 1971; Sieberth, Bulla, Hübner, Mennicken & Sieman, 1971; Müller, Geldmacher & Geldmacher-

v. Mallinckrodt, 1972; Staak, Springer, Besserer & Moosmayer, 1973; Windorfer, Gädeke & Schindra, 1973; Töllner & Pohland, 1976; Lachmann, 1977; v. Mühlendahl & Krienke, 1979; v. Mühlendahl, Kahn & Krienke, 1979).

Eighty to ninety per cent of cases are caused by intoxication with aminophenazone, the most frequently prescribed drug. One fatal case following intravenous injection of metamizole is doubtlessly attributable to an anaphylactic reaction, as merely 0.2 g was injected (Hess, 1950).

A survey of the incidence and the data reported for severe and fatal intoxication with pyrazolones in the German literature is given in Figure 1.
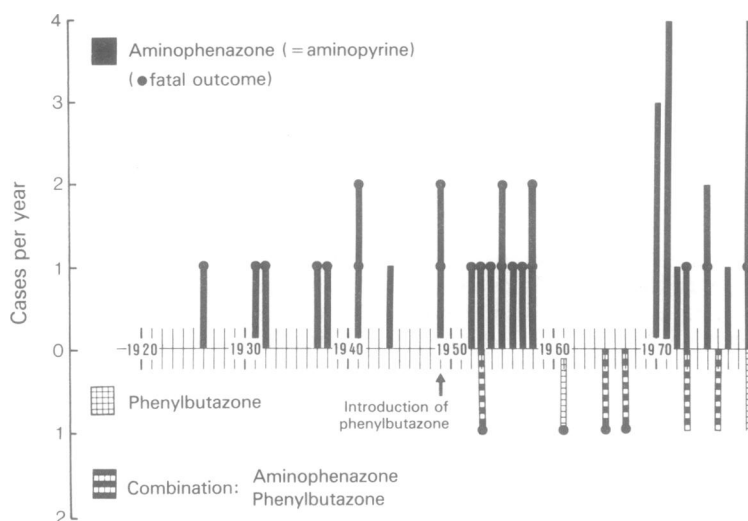
Chemical analysis

Confirmation of pyrazolone intoxication may be possible with a screening test with Phenistix® on the urine. This test stick reacts to produce a colour change from light yellow to violet in the presence of phenolic substances (Geldmacher-v. Mallinckrodt, 1976). However, this test is non-specific and many other drugs and metabolites (for example, salicylate) will also react. For quantitative analysis several procedures are suitable (Clarke, 1969; Sioufi & Marfil, 1978).

Toxicity

Fatal intoxication with aminophenazone may occur

Table 1 Generic names and the most important German proprietary names of pyrazolones; since 1978 aminophenazone has been replaced by propyphenazone

Propyphenazone (until 1978 aminophenazone = aminopyrine)	Metamizole (= dipyrone)	Phenylbutazone	Oxyphenbutazone	Propyphenazone + phenylbutazone
Optalidon®	Novalgin®	Butazolidin®	Tanderil®	Irgapyrin®
Spasmo-Cibalgin®	Baralgin®	Demoplas®	Phlogase®	
Cibalen®	Dolo-Buscopan®	Elmedal®		
Melabon®	Dolorgiet® Tabl.			
Saridon®				
Fortalidon®				

Figure 1 Severe and lethal intoxication by pyrazolones published in the German literature from 1920 to 1979.

in small children after 1–3 g and in infants after 0.7–1.3 g (v. Mühlendahl et al., 1979). Infants apparently exhibit a low tolerance to pyrazolones. Von Mühlendahl & Krienke (1979) have mentioned 28 cases of severe intoxication with the aminophenazone-containing Spasmo-Cibalgin® after the parents had given the infants 0.5 to 1 adult suppository; three children died. For propyphenazone the exact figures are not known. A 16-month-old girl died after the ingestion of metamizole 2.7 g plus quinine 0.9 g (M. Kramer & W. Pola, personal communication).

There have only been isolated reports of severe acute intoxication with phenylbutazone. A 19-month-old child died after phenylbutazone 5 g (cited from Clarke, 1969), whereas a 21-month-old child survived 2.2 g but developed toxic hepatitis (v. Mühlendahl et al., 1979). Similar toxicity can be assumed for oxyphenbutazone.

Signs and symptoms

The symptoms of acute pyrazolone intoxication are similar for all substances of this group. There are, however, differences in severity; pyrazolone derivatives have a particularly adverse effect on the central nervous system and the heart whereas with pyrazolidine derivatives liver damage predominates (Figure 2).

The first life-threatening symptoms are progressive impairment of consciousness with coma and convulsions. Convulsions always indicate severe, potentially fatal intoxication.

Sudden respiratory arrest can ensue in this acute phase of intoxication, followed in some cases by cardiac arrest. Cardiac arrest is not exclusively the result of hypoxia but is also attributable to a direct toxic action on the conduction system and myocardium (Ibe et al., 1967).
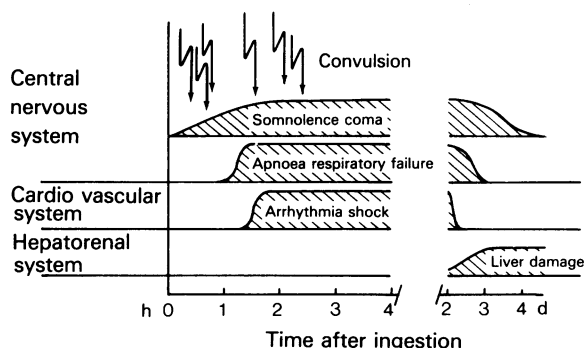
Figure 2. Time course of signs and symptoms of severe pyrazolone intoxication.

After a latent period of 12–24 h, liver cell necrosis may occur. Following ingestion of phenylbutazone, liver damage can be the only manifestation of intoxication. At this late phase a red discoloration of the urine by the pyrazolone metabolite rubazonic acid may be observed.

The side-effects of pyrazolones given in therapeutic doses are different to those described for excessive doses in the toxic range.

Standard therapy

Therapy of acute intoxication consists on the one hand of non-specific life-maintaining measures of critical care medicine and on the other of elimination of the poison. Treatment starts with induction of vomiting or gastric lavage, instillation of medicinal charcoal, and induction of diarrhoea or gut lavage.

Opinions differ on the value of measures to enhance the elimination of pyrazolones from blood and tissue. However, there is no argument that forced diuresis is of no value. All pyrazolones are extensively metabolized and so little is eliminated unchanged by the kidney (1–5%) that forced diuresis cannot hope to be effective. Furthermore, there is the danger in particular with phenylbutazone and oxyphenbutazone of salt and water retention which may lead to hypervolaemia and cardiac failure.

There is insufficient clinical evidence to assess the efficacy of haemodialysis and haemoperfusion. Sieberth *et al.* (1971) have used haemodialysis in severe cases of aminophenazone poisoning with apparent success; however, they did not indicate clearances or the total quantities eliminated. In assessing the efficacy of haemodialysis or haemoperfusion it is necessary to consider pharmacokinetic data (Table 2) and the results of *in vitro* studies (Figure 3–7). Propyphenazone, phenylbutazone and oxyphenbutazone are poorly soluble in water (Koch, 1979; Sunshine, 1969) and phenylbutazone and oxyphenbutazone are, furthermore, highly protein-bound (Coper, 1972; Sjöholm & Sjödin, 1972; Wunderly, 1960) and haemodialysis is unlikely to be effective. Aminophenazone is slightly and metamizole or its hydrolysis product 4-methyl-aminoantipyrine are freely soluble in water (Sunshine, 1969).

Haemoperfusion

In contrast to haemodialysis, haemoperfusion is able to eliminate even highly protein-bound substances from the blood by adsorption, for example, the digitalis glycoside digitoxin (97% protein-bound) (Gilfrich, Okonek, Manns & Schuster, 1978).

Table 2 Physical and pharmacokinetic data of pyrazolones

	Water solubility	Plasma protein binding (%)	Plasma half-life (hours)	Volume of distribution (l/kg)	Plasma clearance (ml/min)
Aminophenazone (= aminopyrine)	s	15–20	2–4	0.7	187
Propyphenazone	sls	?	1–2	1.3	700
Metamizole (= dipyrone)	fs	Hydrolysis product 4-methylaminoantipyrine: no data available			
Phenylbutazone	sls	92–98	60–72	0.2	2.5
Oxyphenbutazone	in	89–92	50–75	0.15	2.0

fs = freely soluble (1–10 solvent: 1 solute).
s = soluble (10–30 solvent: 1 solute).
sls = slightly soluble (100–1000 solvent: 1 solute).
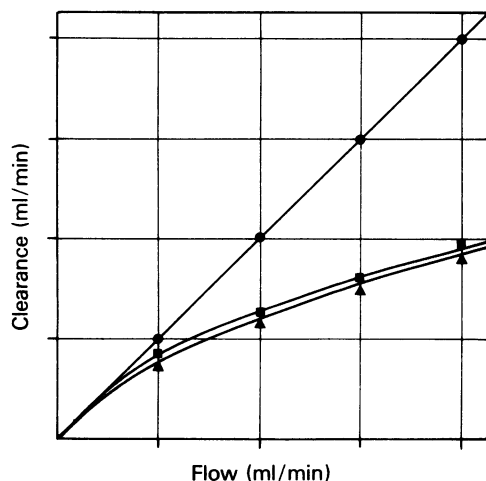in = insoluble (>10 000 solvent: 1 solute).

Figure 3 Clearances (ml/min) of aminophenazone as a function of the adsorbent material (●, resin amberlite XAD-4, 100%; ■, cellulose coated activated charcoal, 85%; ▲, acrylic hydrogel coated activated charcoal, 78%) and blood flow rates (1.25, 2.50, 3.75, 5.00 ml/min); relative clearances (per cent of blood flow) calculated at a blood flow rate of 1.25 ml/min.
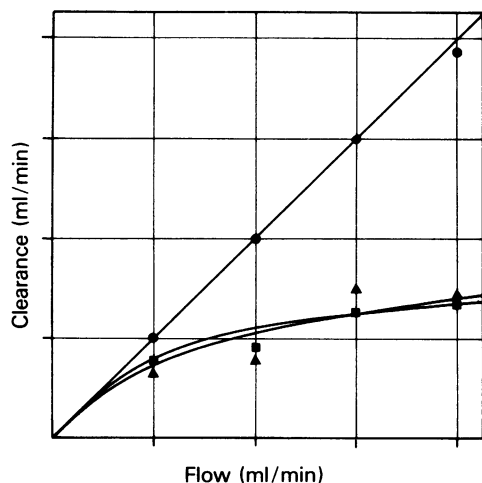

Figure 4 Clearances of propyphenazone; for further explanation refer to Fig. 3. Respective percentages: 100, 79 and 70%.

Figure 5 Clearances of metamizole; for further explanation refer to Fig. 3. Respective percentages: 100, 88 and 72%.

Figure 6 Clearances of phenylbutazone; for further explanation refer to Fig. 3. Respective percentages 33, 11 and 16%.

In order to obtain more information for evaluation of the efficacy of haemoperfusion, in vitro trials were carried out and the adsorption kinetics of pyrazolones determined as a function of the adsorbent material. A miniature haemoperfusion system was used: 13 g of adsorbent was perfused with human blood containing the pyrazolone; flow rates were increased stepwise from 1.25 to 2.5, 3.75 and 5.0 ml/min (Okonek, Reininghaus, Setyadharma & Gaudron, 1980).
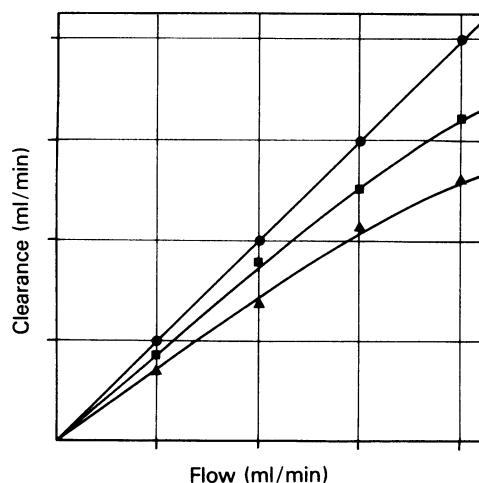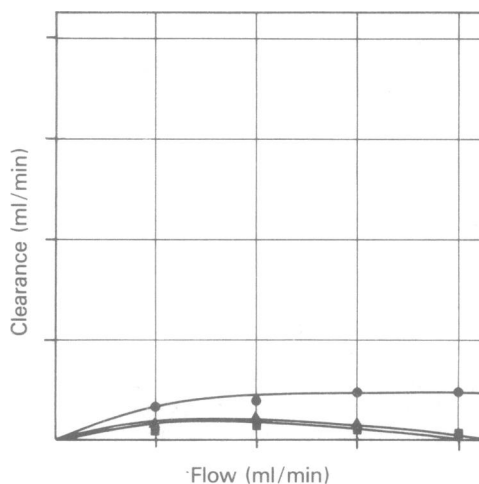
From the differences in concentration before and after the haemoperfusion column and from the blood flow rate, relative clearances (percentage of blood flow) were calculated. At a blood flow rate of 1.25 ml/min, the same relative clearances were obtained as with clinical haemoperfusion systems containing 300–355 g of the adsorbent. The quantitative analyses for aminophenazone and propyphena--zone were carried out using gas-chromatography. The determinations of metamizole or its metabolite 4-methyl-aminoantipyrine, of phenylbutazone and oxyphenbutazone were carried out using thin-layer chromatography. The relative clearances
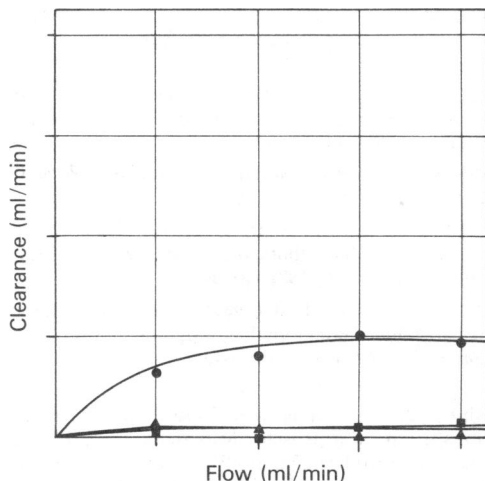
Figure 7 Clearances of oxyphenbutazone; for further explanation refer to Fig. 3.

calculated at a flow rate of 1.25 ml/min and the adsorption kinetics show that elimination by haemoperfusion differs widely for the various pyrazolones. There is a good correlation between adsorption and protein-binding. The weakly protein-bound pyrazolone derivatives (aminophenazone, propyphenazone and metamizole are very well adsorbed. The clearances are 70–100% of the blood flow. The clearance by the uncoated amberlite XAD-4 resin is superior to that of cellulose-coated or acrylic hydrogel-coated activated charcoal (Figures 3–5).

Elimination by haemoperfusion of the pyrazolidine derivatives (phenylbutazone, oxyphenbutazone) is, in contrast, less effective. Perhaps as a result of the high protein binding the clearance by XAD-4 was 33-67% of the blood flow, whereas the coated activated charcoals were relatively ineffective (6–16%) (Figures 6 and 7).

These clearances are only a measure of adsorption; they do not indicate whether toxicologically relevant quantities of the pyrazolones can be eliminated from the body. This question can only be finally clarified by investigations on poisoned patients. However, the pharmacokinetic data has some predictive value. All pyrazolones have a relatively small distribution volume (Aarbakke, 1978; Brune, 1978; Faigle & Dieterle, 1977; Stelzer, 1974; Volz & Kellner, 1979). The distribution volumes of phenylbutazone and oxyphenbutazone are less than 0.3 l/kg so that the highest concentrations are present in the blood and are available for elimination by haemoperfusion; their long plasma half-lives (Aarbakke, 1978; Brune, 1978; Faigle & Dieterle, 1977; Stelzer, 1974) and low endogenous plasma clearances are further factors in favour of the value of haemoperfusion.

It may be concluded that haemoperfusion is effective in intoxication with pyrazolones and may be used in addition to standard therapeutic measures in cases with a poor prognosis.

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Discussion

PROFESSOR MANNAIONI asked Professor Okonek whether he measured free drug in the plasma. Protein binding was a saturable mechanism, so in acute poisoning all the binding sites in albumin might be saturated. If so, diuresis ought to be useful.

PROFESSOR OKONEK replied that even when there was low protein binding, as with aminophenazone, only a small amount of the drug is eliminated by the kidneys — between one and five per cent. It was extensively metabolised. Both factors were reasons for not using forced diuresis. In addition there was the danger of water retention. He knew of no investigations which could answer Professor Mannaioni's question.

PROFESSOR MIESCHER asked whether plasmapheresis would be worth trying for drugs which are closely bound to proteins.

PROFESSOR OKONEK said it was a possibility as was plasma separation but there was no experience yet.